

The **EX**tremity **C**onstraint- **I**nduced **T**herapy **E**valuation

The **EXCITE** Randomized Clinical Trial

Funded by: The National Center for
Medical Rehabilitation Research
(NCMRR) of the National Institute for
Child Health and Human Development
and NINDS (NIH)

The Investigator Team

- **Co Principal Investigators**

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- **Director, Data Management Center**

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The Investigator Team

■ Site Principal Investigators

- **Kathye Light**, Ph.D., P.T. (University of Florida)
- **Carol Giuliani**, Ph.D., P.T. (University of North Carolina) and **David Good**, MD (Wake Forest University, North Carolina)
- **Gitendra Uswatte**, Ph.D. and **Edward Taub**, Ph.D. (University of Alabama at Birmingham)
- **Deborah Nichols**, Ph.D., P.T. (The Ohio State University)

Constraint Induced Movement Therapy (Forced Use)

■ Collaborators

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■ Graduate Students

- Carol Ostendorf, M.Ms.P.T.
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- Amy Piancetino, M.P.T.
- Marcy Swanson, DPT
- Jill McJunkin, DPT

The **EXCITE** Trial: Historical Perspectives

- February 1996: Taub and Wolf make presentation to American Physical Therapy Association (APTA) Neurology Section
- 1996 periodic conference calls
- February 1997: Wolf asks Neurology Section for \$6000
- May 1997: planning meeting at Emory
- **June 1997: Wolf and Miller meet with NCMRR**
- July 1997 standardization of Constraint-Induced Therapy (CIT) application at UAB

The **EXCITE** Trial: Historical Perspectives

- Letter of Intent
 - Overview
 - Timeline
 - Budgets
- Permission/Approval
- Keeping costs down – agreed to maximum

Establishing a Clinical Research Agenda: Basis for Seeking Funding

■ I. Concept

■ A. Original or response to Request for Application (RFA), (Line 2)

- “helping the CSR”

■ B. Personnel

- Track record
- Past productivity
- Past training including post-doc experience

Establishing a Clinical Research Agenda: Basis for Seeking Funding

- Ia. Collaborations/referrals
 - A. Resource personnel
 - B. Clinical research experience
 - Relevance to specific aims
 - C. Defining the collaboration
 - Establishing fiscal responsibilities/commitments
 - Resources and environment
 - Teamwork and output information dissemination

Establishing a Clinical Research Agenda: Basis for Seeking Funding

II. DESIGNING PROTOCOLS

- Don't be afraid to ask.....
 - colleagues, biostatisticians
 - non-academics
- What will set you apart?; that is: what is **unique** or **innovative** about your idea and should that uniqueness be noted in your protocol?
- To avoid pitfalls:
 - Think!!!!
 - Be critical of input!
 - Once completed – start over!
 - Repeat and refine

Establishing a Clinical Research Agenda: Basis for Seeking Funding

■ III. The “Unknowns”

- A. Biosketch – selling job!
- B. Appendices and support
- C. THINK AS A REVIEWER, NOT AS AN APPLICANT
 - 10-14 REVISIONS
- D. If it ain't ready, don't' submit!
 - Don't wait until the last minute (e.g. our next TC grant)
- E. Persistence
- F. Talk with project officer – your friend!

The **EXCITE** Trial: Historical Perspectives

- August-December 1997: pilot data acquisition from 14 subjects across 7 sites
- January 1998 - February 1998: analyze data (Taub and Miller), write narrative (Wolf and Taub) {statistical section: Miller; site specific information: site PIs}
- late February 1998: decide grant not ready for March 1 deadline

The **EXCITE** Trial: Historical Perspective

- June 1, 1998: submit grant
- November 1998: telephone conference call
- December 31, 1998: receive grant reviews
- January - February 1999: Wolf, Taub, and Miller respond to critiques, rewrite, and get updated information from site PIs
- March 1, 1999: grant resubmitted
- May 5, 1999: reverse site visit conf. call

Recruitment Summary

EXCITE RECRUITMENT EFFORTS SUMMARY: JUNE 2000-2002

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COMPOSITE ACROSS SITES

Site	TH	TL	TF	AP	SS	NI	TP	HS	MS	MP	SI	OP	EXCITE
EU	246	155	199	24	113	37	100	5	44	31	24	120	40
UAB	100	53	27	5	34	28	16					169	39
UFL	37	44	257	1	30	20	13	1	15	11	0	30	39
OSU	64	76	107	29	54	70	30	18	4	97	17	24	29
USC	10	34	129	3	10	16	1	0	3	11	5	22	42
UNC	58	38	103	3	84	64	52	6	21	39	2	36	18
WF	20	10	22	6	2	2	8		2	5		6	15
TOTAL	533	408	844	71	327	235	218	30	89	194	48	407	222

TH: too high (533)

TL: too low (408)

TF: too far post injury (844)

AP: aphasia (71)

SS: second/multiple strokes (327)

NI: not interested (235)

TP: transport problems (218)

HS: hemorrhagic (30)

MS: mental status (89)

MP: medical problems (194)

SI: spasticity excessive (48)

OP: other problems (no show, not stroke) (407)

EXCITE: LESSONS LEARNED

■ **Coordination**

- Thankless and time consuming
- Strong oversight

■ **Recruitment**

- Time consuming
- Rehab versus pharmacological clinical trials
- Catastrophic injury versus non-catastrophic
- Transportation

EXCITE: LESSONS LEARNED

- **Psychosocial**
 - Acute versus sub-acute versus chronic
 - Family dynamics
 - Cultural perspectives
- **Administrative**
 - Manual of Procedures (MOP)
 - Adherence to procedures
 - Fore-play or is it fore-planning (perhaps both?)
- **Adverse events monitoring and reporting**
- **Data Safety and Monitoring Board**
 - Advise and guidance
- **Information and dissemination**

Future Research Perspectives

www.excite.emory.edu

COMPONENTS:

A. **Interventional**

- A. Physical (S. Wolf et al) [NCMRR, NIH: HD/NS 37606]
- B. Behavioral
 - A. Caregiver (P. Clark et al) [NIH: NR07612]
 - B. Clinician
- C. Virtual Environment (New Jersey)
 - A. Neuroimaging (Butler)
- D. Visual imagery (Butler) [NIH, R21 pending]

B. **Mechanistic**

- A. Neuroimaging/TMS (EXCITE) (D. Good et al) [NIH: HD40984] (Emory: K. Sathian, S. Wolf, A. Butler, H. Mao)
- B. Biomechanics (EXCITE) (J. Alberts) (VA Merit Review, NIH R21, pending)
- C. Molecular – Biomarkers as precursors to neuronal reorganization

Constraint Induced Movement Therapy (**EXCITE** Trial)

- Minimal Motor Criteria
 - Higher Functioning
 - $>20^{\circ}$ wrist extension; $>10^{\circ}$ extension of all digits
 - Lower Functioning
 - $>10^{\circ}$ wrist extension; . 10° thumb and two other digits
 - Performance x3 in 1 minute

The **EXCITE** Trial: Inclusion/Exclusion Criteria

INCLUSION:

- Minimal motor criteria: higher and lower functioning
- Willingness to participate; signed informed consent
- Not excluded if have somatosensory deficits
- Any type of previous rehab interventions
- < 2.5 Motor activity log (MAL)

The **EXCITE** Trial:

Inclusion/Exclusion Criteria

EXCLUSION:

- Under the age of 18
- Terminal illnesses
- Intent to move or relocate too far away
- Present pharmacological therapy
- Intended pharmacological therapy
- Not meet minimal motor criteria
- Extreme aphasia or mental incompetence

The **EXCITE** Trial: Overview

- Primary outcome measures (developed by Taub et al. at UAB):
 - Modification of the Emory Motor Function Test (Wolf Motor Function Test)
 - Motor Activity Log (MAL)

The **EXCITE** Trial: Primary Outcome Measures

Wolf Motor Function Test (WMFT)

impaired-based, laboratory and real-world measures designed to examine segmental and inter-segmental movements

Motor Activity Log (MAL)

30 real world measures typically performed in the home environment

The **EXCITE** Trial: Overview (continued)

Secondary outcome measures:

- Actual Amount of Use Test (AAUT) {Taub et al.}: real-world measure of spontaneous use of limb (videotaped)
- Accelerometry:
- Stroke Impact Scale {Duncan et al}: 64 items, 8 domains: strength, hand function, combined Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), mobility, memory, communications, **emotion**, socialization

The **EXCITE** Trial: Pilot Data

- 9 higher, 5 lower level functioning stroke subjects
- MAL Dose-response curves over 10 days of treatment (repeated measures ANOVA with functioning level as between subject variable and Rx day as within subject variable)
 - Functioning levels and treatment day were significant effects but no interaction (similar shaped curves with rate of change showing negative acceleration)
 - Persistence in scores at 3 month follow -up
- Caregiver responses in parallel

The **EXCITE** Trial: Essential Considerations

- Blinded, cross-over trial
- N = 240 sub-acute (3-6 month post-stroke subjects) across 6 sites (40 per site)
- Attempts at equal distribution of higher and lower functioning subjects
- Control group: usual and customary care

The **EXCITE** Trial:

The Intervention

- Wearing hand splint - no thumb opposition
 - 90% of waking hours, 6 hrs/day (interventionist), 14 consecutive days
 - Splint off: water based functions, naps or agreed to circumstances
- Mass Practice of Functional Activities
 - Appropriate sequencing of task and components

The **EXCITE** Trial:

Specific Aims

Specific Aim 1:

- Can a 2-week Constraint Induced (CI) Therapy program be applied successfully to patients with sub-acute stroke in multiple settings?
 - Between subject factors (functioning level and group assignment)
 - Within subject factor (time: 4, 8 and 12 months)
- Major point: Test of differences between groups at 12 months *within* each functioning level (higher/lower)
- Secondary analysis: Rx x time interaction: time course over the first year post-Rx is same between groups

The **EXCITE** Trial:

Specific Aims

Specific Aim 2:

- Do the therapeutic gains achieved through CI therapy persist over time? (12-24 months)
 - Secondary analyses: (time dependent covariates: new stroke events; general physical ability; as in Specific Aim 1)

The **EXCITE** Trial:

Specific Aims

Specific Aim 3:

- Does the initial level of motor ability (higher/lower functioning) determine the extent to which sub-acute stroke patients improve with CI Therapy?
 - *Between* levels of functioning analyses

The **EXCITE** Trial:

Specific Aims

Specific Aim 4:

- Is the magnitude of response to CI Therapy different among patients with sub-acute stroke and chronic stroke?
 - 3-6 months versus 15-18 months post-stroke
 - Makes use of control group that has been formally randomized
 - Compares BL, 4, 8, 12-month MAL and WMFT scores to 12, 16, 20, 24 month scores for delayed RX group functioning analyses